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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/766,421	01/27/2004	Masatake Kudoh	14879-090002	4485
26161	7590	05/05/2005	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			PAK, YONG D	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 05/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/766,421	KUDOH ET AL.	
	Examiner	Art Unit	
	Yong D Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11/24/2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 15-21 and 23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 15-21 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/978,758.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>11/24/2004</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This application is a divisional of 09/978,758, now issued as U.S. Patent No. 6,706,507, which is a CIP of PCT/JP01/01082.

The preliminary amendment filed on March 8, 2004, canceling claims 1-14, 22 and 24, amending claims 15 and 23, has been entered.

Claims 15-21 and 23 are pending and are under consideration.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

However, the foreign application JAPAN 2000-43506 filed on February 16, 2000 upon which priority is claimed fails to provide adequate support for claim 16 of this application. The foreign application describes a microorganism that naturally produces (R)-2-octanol dehydrogenase but does not describe a host cell transformed with a vector comprising a polynucleotide encoding a (R)-2-octanol dehydrogenase.

Therefore, the effective filing date for purpose of prior art of claim 16 is the filing date of JAPAN 2000-374593, which is December 8, 2000.

Information Disclosure Statement

The information disclosure statement s(IDS) submitted on January 27, 2004 and November 2004 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Specification

Examiner notes that applicants have not updated the relationship of the instant application to its parent application (09/978,758) that has matured into a U.S. patent (U.S. Patent No. 6,706,507). Examiner urges applicants to amend said information by providing the parent application number and its U.S. patent number in response to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 and 23 and claims 16-21 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 23 recite the phrase "processed product of the microorganism". The metes and bounds of this phrase is not clear to the Examiner. The phrase can encompass a wide variety of "processed products". It is also not clear what activities

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these "processed products" have. Therefore, it is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above phrase.

Claims 15 and 23 and claims 16-21 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 23 recite the phrases "preferentially oxidizes (R)-2-octanol". The metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. It is not clear to the Examiner as to how much of an oxidation of a (R)-2-octanol as compared to (S)-2-octanol is considered as "preferentially" oxidizing (R)-2-octanol by the applicants. A perusal of the specification did not provide a clear definition for the above phrase. Without a clear definition in terms of numerical value, those skilled in the art would be unable to conclude a polypeptide that "preferentially oxidizes (R)-2-octanol".

Claims 15 and 18 and claims 16-21 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 18 recite the phrase "alcohol". The metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. It is not clear to the Examiner what types of alcohol are encompassed in the claims.

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Claims 15 and 18 and claims 16-21 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 18 recite the phrase "a microorganism". The metes and bounds of the phrase in the context of the above claim is not clear to the Examiner. It is not clear to the Examiner what types of microorganism are encompassed in the claims.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites the phrase "alcohol is (S)-4-chloro-3-hydroxybutyric acid ethyl ester". It is not clear how an alcohol can be an ester.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-21 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15-21 and 23 are drawn to a method for the producing any alcohol by using a (R)-2-octanol dehydrogenase or any or all microorganism producing or expressing a (R)-2-octanol dehydrogenase or any treated products of said microorganism. The claims encompass a method for producing any alcohol by using recombinants, variants and mutants of any (R)-2-octanol dehydrogenase, any or all microorganisms producing recombinants, variants and mutants of any (R)-2-octanol dehydrogenase or any treated products of said microorganisms. Therefore, the claims are drawn to a method of producing any alcohol using any dehydrogenase having any structure or produced by any or all microorganism. The specification only teaches two examples, a method of producing (S)4-chloro-3-hydroxybutyric acid ethyl ester or a propoxybenzene using a microorganism producing a (R)-2-octanol dehydrogenase of SEQ ID NO:2. These few examples are not enough and does not constitute a representative number of species to describe the whole genus there is no evidence on the record of the relationship between the structure of a (R)-2-octanol dehydrogenase of SEQ ID NO:2 and the structure of any recombinants, variants and mutants of any (R)-2-octanol dehydrogenase. Therefore, the specification fails to describe the structure of the genus comprising variants and mutants of any (R)-2-octanol dehydrogenase, genus comprising any substrates and a genus comprising any microorganism producing (R)-2-octanol dehydrogenase used in a method for producing any alcohol. Furthermore, the specification does not provide the function of the treated product of the microorganisms.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention

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in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 15-21 and 23.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 15-21 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the producing a (S)4-chloro-3-hydroxybutyric acid ethyl ester or a propoxybenzene using a (R)-2-octanol dehydrogenase of SEQ ID NO:2 or a transformant producing said enzyme, does not reasonably provide enablement for a method for the production of any or all alcohol using mutants and variants of any or all (R)-2-octanol dehydrogenase, or any microorganism producing mutants and variants of any or all (R)-2-octanol dehydrogenase or using any treated products of any microorganism producing (R)-2-octanol dehydrogenase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in

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the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 15-21 and 23 are drawn to a method for the producing any alcohol by using a (R)-2-octanol dehydrogenase and a microorganism producing or expressing a (R)-2-octanol dehydrogenase. The claims encompass a method for producing any alcohol by using recombinants, variants and mutants of any (R)-2-octanol dehydrogenase, a microorganism producing recombinants, variants and mutants of any (R)-2-octanol dehydrogenase or any compounds produced by a microorganism producing (R)-2-octanol dehydrogenase. Therefore, the claims are drawn to a method of producing any alcohol using any substrates or ketones and any (R)-2-octanol dehydrogenase having any structure. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of (R)-2-octanol dehydrogenase variants and mutants and substrates, broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a method of producing a (S)-4-chloro-3-hydroxybutyric acid ethyl ester or a propoxybenzene using the (R)-2-octanol dehydrogenase of SEQ ID NO:2 or a host cell producing said enzyme.

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It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of any (R)-2-octanol dehydrogenase. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptide, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method for the production of alcohol from any or all substrates or ketones using any or all mutants and variants of any (R)-2-octanol dehydrogenase, a microorganism producing any or all mutants and variants of any (R)-2-octanol dehydrogenase or any or all products of a microorganism producing a (R)-2-octanol dehydrogenase, because the specification does not establish: (A) regions of the (R)-2-octanol dehydrogenase structure which may be modified without affecting (R)-2-octanol

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dehydrogenase activity; (B) the general tolerance of (R)-2-octanol dehydrogenase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; (D) oxidizing any substrates or ketones with a (R)-2-octanol dehydrogenase to produce any alcohol; (E) using any products of a microorganism producing (R)-2-octanol dehydrogenase to produce an alcohol; and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method for the production of any alcohol using any substrates and variants and mutants of any (R)-2-octanol dehydrogenase, a microorganism producing variants and mutants of any (R)-2-octanol dehydrogenase and a product of a microorganism producing (R)-2-octanol dehydrogenase. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of which (R)-2-octanol dehydrogenase and substrates to use to produce an alcohol is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 15, 17-19, 21 and 23 are rejected under 35 U.S.C. 102(b) as anticipated by Kise et al. (see rejection of “derivative” under 35 U.S.C. 112, 2nd paragraph).

Claims 15, 17-19 and 21 are drawn to a method for producing (S)-4-chloro-3-hydroxybutyric acid ethyl ester by reacting an NAD⁺ dependent (R)-2-octanol dehydrogenase having the recited properties recited in claim 15 with 4-chloroacetoacetic acid ethyl ester. Claim 23 is drawn to a method for producing optically active alcohol.

Kise et al. (JP 01-277494 – reference form PTO-892) discloses a method for producing an optically active alcohol by reacting an NADH dependent (R)-2-octanol dehydrogenase with 4-chloroacetoacetic acid ethyl ester (abstract – English Translation of JP 01-277494 – form PTO-892). The dehydrogenase of Kise et al. also oxidizes (R)-2-octanol (abstract – Derwent English Translation – form PTO-892). Therefore, the reference of Kise anticipates claims 15, 17-19, 21 and 23.

Claim 16 is rejected under 35 U.S.C. 102(e) as anticipated by Bommanus et al.

Claim 16 is drawn to a method for producing an alcohol by with a host cell transformed with a vector comprising a polynucleotide encoding a (R)-2-octanol dehydrogenase having the recited properties recited in claim 15.

Bommanus et al. (U.S. Patent Application Pub. No. 2003/0054520 - form PTO-892) discloses a method for producing an alcohol with a (R)-alcohol dehydrogenase which uses NADH (Column 2). Even though Bommanus et al. does not explicitly disclose that the enzyme produces (S)-4-halo-3-hydroxybutyric acid esters by reducing 4-haloacetoacetic acid esters, the enzyme inherently possess this activity since the enzyme catalyzes (R)-2-octanol and (R)-2-octanol and 4-haloacetoacetic acid ester have similar structure, such as carbon chain length. Therefore, the reference of Bommanus et al. anticipates claim 16.

Since the Office does not have facilities for examining and comparing applicant's polypeptide with the polypeptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the product claimed in the method and the product of the method of the prior art (i.e., that the protein of the prior art does not possess the same material structure and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kise et al. in view of ChemExper.

Claims 20 is drawn to a method for producing 2,3-difluoro-6-nitro[[(R)-2-hydroxypropyl]oxy]benzene by reacting an NAD⁺ dependent (R)-2-octanol dehydrogenase having the recited properties recited in claim 15 with 2-acetonyloxy-3,4-difluoronitrobenzene.

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The reference of Kise et al. teaches a method of producing optically active alcohols by using a dehydrogenase, as discussed above. Kise et al. also teaches that the dehydrogenase oxidizes ketones and one having ordinary skill in the art would have recognized the ability of the dehydrogenase of Kise et al. to reduce other ketones.

The reference of Kise al. does not teach a method of producing 2,3-difluoro-6-nitro[[(R)-2-hydroxypropyl]oxy]benzene from 2-acetonyloxy-3,4-difluoronitrobenzene.

2-acetonyloxy-3,4-difluoronitrobenzene is available via commercial chemical catalogs, such as ChemExper (form PTO-892).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use the dehydrogenase of Kise et al. to produce other ketones, such as 2-acetonyloxy-3,4-difluoronitrobenzene, which is commercially available. One having ordinary skill in the art would have been motivated to use the dehydrogenase of Kise et al. to reduce such ketones to produce optically active alcohols on a large scale. One of ordinary skill in the art would have had a reasonable expectation of success since Kise et al. teaches a dehydrogenase which reduces ketones to optically active alcohols and a method of producing optically active alcohols.

Therefore, Kise et al. renders claim 20 *prima facie* obvious to those skilled in the art.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

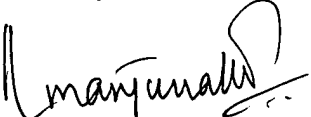
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax

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phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652



Manjunath Rao
Primary Examiner 1652